

Synthesis of Schiff Bases, Supramolecular Complexes and their Influence on Macrophages

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Abstract: New Schiff bases of gossypol were synthesized and their supramolecular complexes with monoammonium salt of glycyrrhizic acid were obtained, the structure was studied in IR and UV spectra. The effect of Schiff's bases and their water-soluble supramolecular complexes on the amount of macrophages in the peritoneal fluid of intact mice was studied at a dose of 10 and 25 mg/kg for 24-48 hours. It was found that the water-soluble supramolecular complexes of Schiff's bases obtained with MASGK increase the number of macrophages.

Key words: Gossypol, Schiff's base, spectrum, biologically active substance, polyphenol, triterpene, aldehyde, naphthalene.

Most Schiff bases synthesized on the basis of gossypol exhibit interferon inducers, immunomodulatory and immunosuppressive properties. According to the results of research conducted in recent years, derivatives of gossypol obtained with amines of different structures have been found to have higher physiological activity compared to gossypol, but it should be said that all synthesized gossypol derivatives are not soluble in water.

The reaction of obtaining primary amine Schiff bases with gossypol is carried out in ethyl alcohol at a temperature of 70-80 °C for 3 hours. The progress of the reaction was monitored by HCV, upon completion of the reaction, the reaction mixture was cooled and left overnight in the refrigerator, and the resulting precipitate was filtered.

The reaction of obtaining Schiff bases of gossypol with primary amines is carried out according to the following scheme:

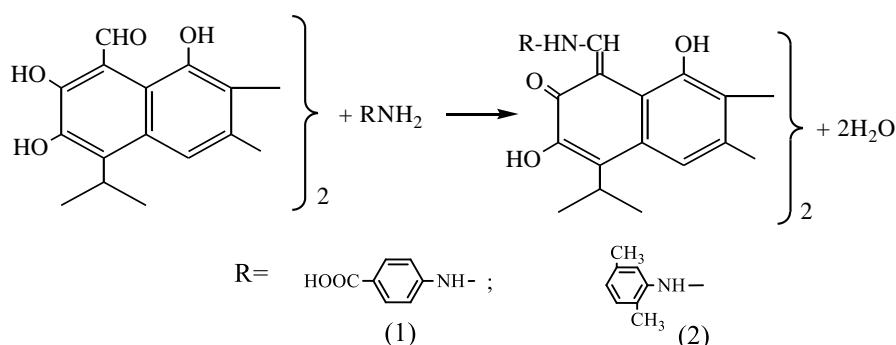


Table 1 Physicochemical properties of synthesized gossypol derivatives

| N ^o | R | Liquid °C | R _f | Reaction yield % | Color | IR spectrum (cm ⁻¹) | UV spectrum λ _{max} HM |
|----------------|---|-----------|----------------|------------------|--------|---------------------------------|---------------------------------|
| I | 1 | 282-283 | 0.56* | 89.2 | yellow | 1623.40;1687.47 | 283;310 |
| II | 2 | 251-252 | 0.64** | 82.3 | yellow | 2319.32; 1722.17 1629.87 | 294;326 |

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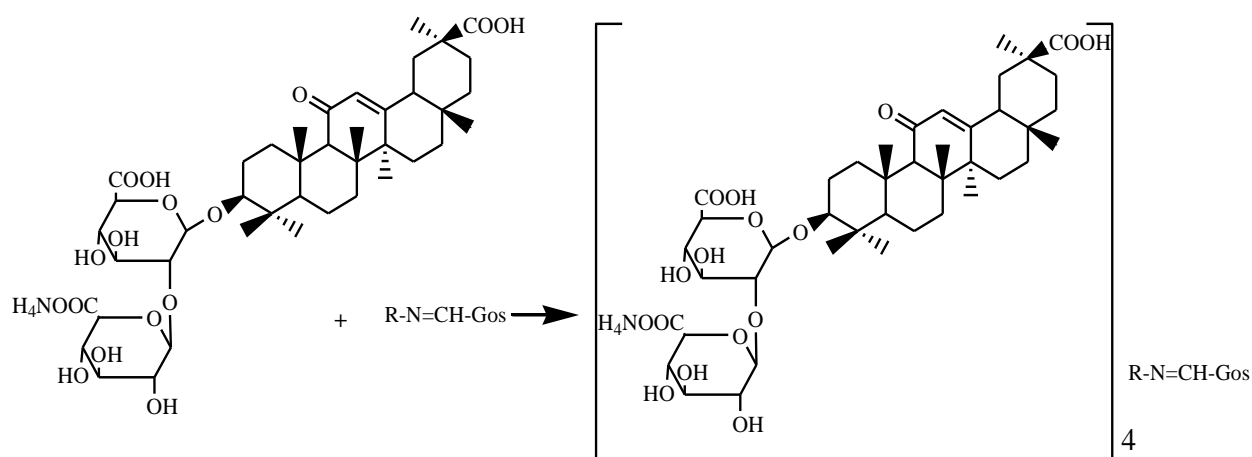


Systems: * hexane-acetone (2:1) ** benzene-acetone (2.5:1)

The obtained Schiff bases gave absorption maxima in the range of 270-350 nm in the UV spectrum. When analyzing the IR spectrum, instead of the valence vibrations of the -CHO group at 1720-1750 cm^{-1} , -CH=NH- and valence vibrations were observed in the range of 1602,8-1687,9 cm^{-1} characteristic of =CH-NH- groups.

GK and MASGK are known to form clathrates with poorly water-soluble drugs and become water-soluble. MASGK is a major triterpene glycoside isolated from the root of the licorice plant and has a number of unique physicochemical properties, one of which is its solubilization property. Therefore, by forming supramolecular complexes with drugs, MASGK dramatically increases their solubility in water, reduces their toxicity, and at the same time provides an opportunity to maintain the effectiveness of action even in very small doses.

Supramolecular complexes of Schiff bases obtained at the next stage of research with MASGK were obtained according to the following scheme:



4 mol of MASGK was dissolved in 50% $\text{C}_2\text{H}_5\text{OH}$, 1 mol of Schiff's base was added to it, and the reaction was carried out at 50-60 $^{\circ}\text{C}$ for 12 hours with constant stirring. Ethyl alcohol was removed from the reaction mixture using a rotary evaporator, and the aqueous portion was lyophilized. The physico-chemical properties of the obtained supramolecular complexes are presented in Table 2.

When MASGK forms supramolecular complexes, the OH and COOH groups in it form a hydrogen bond and enable joining. In addition, the hydrophobic part of MASGK is affected by the hydrophobic parts of gossypol derivatives.

Table 2 Some physico-chemical properties of the received supramolecular complexes

| No | Schiff base | Ratio | Liquid $^{\circ}\text{C}$ | R_f | Reaction yield % | IR spectrum (cm^{-1}) | UV spectrum λ_{max} HM |
|-----|-------------|-------|---------------------------|-------|------------------|----------------------------------|---------------------------------------|
| III | I | 1:4 | 212-213 | 0.33 | 91.6 | 1711.34;1625.1 7 | 272;422 |
| IV | II | 1:4 | 204-205 | 0.67 | 92.4 | 1722.17;1632.6 2 2862.74 | 249;443 |

System: Hexane-acetone (1.5:1)

When the UV and IR spectra of the obtained supramolecular complexes were analyzed, it was revealed that the signals in the spectrum of Schiff bases were broadened due to the hydrogen bonds in the complex compounds.

At the next stage of the research, it was determined that the obtained substances affect the amount of macrophages depending on their dose in 24- and 48-hour dynamics in vivo in intact mice.



The activity of the compounds was studied in mice weighing 20±2 g by a single oral dose of 10 and 25 mg/kg. 5 mice were taken for each investigation. After 24 and 48 hours, the animals were decapitated. The thymus, lymph nodes, and sclera of mice were removed, weighed, and cell fluid was prepared in isotonic sodium chloride solution (20 ml per 100 mg of organ mass). Nucleated cells were detected by microscopy in a Goryaev chamber, where a sample of cells was prepared by 20-fold dilution in 3% acetic acid solution. After decapitation, the abdomen was opened and 0,02 ml of exudate was collected using a Sali pipette and added to 0,4 ml of 3% acetic acid solution. Calculations were carried out in all large squares.

The amount of macrophages in the peritoneal fluid of intact mice was found to be 90±11x10⁶/ml.

Administration of 10 mg/kg of MASGK increased the number of macrophages to 322±28 and 317±25x10⁹/ml after 24 and 48 hours, respectively, with a stimulation index (SI) of 3,6 and 3,5. MASGK at a dose of 25 mg/kg did not affect the amount of macrophages in the peritoneal fluid.

After administration of gossypol at a dose of 10 mg/kg, the number of macrophages increased to 182±15x10⁹/ml after 24 hours and 150±12x10⁹/ml after 48 hours. It showed that SI was equal to 2,0 and 1,7. Increasing the dose of gossypol to 25 mg/kg resulted in an increased effect. Thus, the maximum effect shifted from 24 hours at 10 mg/kg to 48 hours at 25 mg/kg.

Table 3 Effect of gossypol, its derivatives and supramolecular complexes with MASGK on the amount of macrophages in peritoneal fluid (M±m; n=5)

| Medicines | Dose / study time / amount of macrophages | | | | | | | |
|-----------|---|-----|---------------------|-----|---------------------|------|---------------------|------|
| | 10 mg/kg | | | | 25 mg/kg | | | |
| | 24 hour | | 48 hour | | 24 hour | | 48 hour | |
| | 10 ⁹ /ml | SI | 10 ⁹ /ml | SI | 10 ⁹ /ml | SI | 10 ⁹ /ml | SI |
| Gossypol | 182±15 | 2,0 | 150±14 | 1,7 | 118±11 | 1,3 | 623±55 | 6,9 |
| MASGK | 322±28 | 3,6 | 317±26 | 3,5 | 91±8,0 | 1,0 | 107±10 | 1,2 |
| I | 367,5±33,2 | 4,1 | 202,5±16,3 | 2,2 | 355±28,3 | 3,9 | 257,5±21,7 | 2,8 |
| II | 207,5±18,4 | 2,3 | 180±14,2 | 2,0 | 157,5±12,8 | 1,75 | 117,5±9,7 | 0,78 |
| III | 350±28,8 | 3,8 | 385±31,2 | 4,2 | 340±29,7 | 3,7 | 465±38,9 | 5,1 |
| IV | 105±8,2 | 0,7 | 550±43,2 | 6,1 | 200±15,5 | 1,3 | 205±12,8 | 2,3 |

Control 90±11x10⁹/мл

Thus, under the influence of the newly synthesized Schiff's bases based on gossypol and their water-soluble supramolecular complexes obtained with MASGK, the number of macrophages in the peritoneal fluid of the mouse gastric cavity significantly increased, and it was shown that it depends not only on their structure, but also on the time of exposure and dose.

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